Brain metastases in HER2-positive breast cancer: challenges and opportunities

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Submitted Oct 01, 2012. Accepted for publication Oct 26, 2012.
DOI: 10.3978/j.issn.2224-5820.2012.10.11
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The development of metastases in the central nervous system (CNS) is one of the most devastating consequences of breast cancer progression (1). Although epidemiologic studies estimate that the incidence of brain metastases (BM) in women with metastatic breast cancer (MBC) is 10-16% (2,3), reports from autopsies suggest rates of up to 30% (2,4,5).

Life expectancy for patients with breast cancer has risen thanks to advances in efficient systemic treatments, such as trastuzumab in HER2-positive patients that together with the detection of subclinical disease, has led to an increase in the incidence of BM (6), which is even greater than hormone receptor-positive tumors. In the RegistHER study, a prospective observational study of 1,012 patients with newly diagnosed HER2-positive MBC, 37.3% of patients developed BM after a median follow-up of 29 months (7). Herein lies the importance of the current interest in determining new therapeutic strategies in patients with BM phenotype HER2-positive, which not only come down to local treatments such as whole brain radiotherapy (WBRT) with its associated late toxicity (8), but which also offer optimal CNS responses.

Why is there more BM in HER2-positive tumors? Some have attributed this to an inherent biological tropism for the CNS independent of treatment and other prognostic factors (9-11). Therefore it is fundamental to identify molecular signatures predictive of organ-specific metastases. The hypothesis of an increase in BM in the post-trastuzumab era has also been proposed, since it does not cross the blood-brain barrier (BBB) similarly in many chemotherapeutic agents used in the conventional treatment of MBC.

In recent years, a limited number of newer chemotherapeutic agents have demonstrated activity in prospective studies of MBC-related BM. Limited activity with temozolomide (12-14) or cisplatin (15-17) has been demonstrated as a single agent or in combination with other chemotherapies and WBRT. Similarly, there are provocative retrospective data with capecitabine, an agent with well established efficacy in breast cancer, which has been proposed to cross the BBB via the human concentrative nucleoside transporter (hCNT) (18,19).

Nevertheless, possibilities are emerging within anti-Her2-therapies: the role of trastuzumab is being considered as a probable radiosensitizer (20,21) or the penetration of the BBB - still unconfirmed for lapatinib (22). Ongoing phase II studies with afatinib (NCT01441596; LUX-breast3), neratinib (NCT01494662) and everolimus (NCT01305941) are trying to find new paradigms in treatments for patients with HER2-positive MBC with BM.

The LANDSCAPE study (23) has emerged in this situation and was published last November in the *The Lancet Oncology*, a phase II study to determinate if patients with HER2-positive MBC associated previously untreated multiple BM who receive lapatinib plus capecitabine can avoid or delay WBRT, support a high objective CNS response (65.9%; 95% CI, 50.1-79.5%) among 44 evaluable patients, and nine patients (20%) had a volumetric reduction of at least 80%. Efficacy with the combination is similar to that with WBRT, but with the possibility of less neurological toxicity. Median time to progression was 5.5 months (95% CI, 4.3-6.0 months) and median time to WBRT of 8.3 months (95% CI, 5.4-9.1 months), which is clinically relevant for a population with short overall survival.

It is important to note that the individual contributions of lapatinib versus capecitabine versus the combination are unknown, as many of these patients had not received prior capecitabine, which appears to have independent CNS activity. Additionally, it is not a comparative study with other therapeutic regimes, such as monotherapy, other combination treatments, and WBRT. A previous study (24) comparing lapatinib plus capecitabine to lapatinib plus topotecan for patients with HER2-positive breast cancer BM progressing after trastuzumab and radiotherapy, was stopped before full enrollment, although marked CNS activity was observed with the combination lapatinib/capecitabine.

In the population studied, 50% were Hormonal Receptor negative (ER negative, PR negative). Taking into consideration the recent Sant Gallen classification, efficacy results of the combination according to hormone receptor expression should be known, since many of them could be classified in the Luminal B phenotype. Furthermore, it is important to control systemic disease. Seven patients (16%) of the study had CNS progression, of which two patients had progression outside of the CNS.

Considered inclusive by the authors, it is necessary to mention the limitations preferentially related to their extrapolation to the general population. More than 95% of all patients presented with Eastern Cooperative Oncology Group performance status of 0-2 and 43% of the patients had asymptomatic BM, which is better than would be expected in an unselected population of patients with BM, without providing quality of life information and neurocognitive functions.

From the pharmacological perspective, no measurement of the concentration of lapatinib or capecitabine in the cerebrospinal fluid has been done, so it is not possible to affirm its penetration of the BBB. Other factors should also be taken consideration such side effects: diarrhea (20%) and hand-foot syndrome (20%) grade 3-4, requiring dose reductions of lapatinib in 16 (36%) of 45 patients and dose reductions of capecitabine were necessary in 26 (58%) of 45 patients.

Considering said limitations, this study can be considered a first important advance in the search for treatment strategies for BM in BMC. The incidence of BM will probably rise within the clinical handling of HER2-positive patients. As a result, it is a necessity to continue research for new drugs focusing on obtaining CNS activity, in addition to sufficient BBB penetration.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Mayer M. A patient perspective on brain metastases in breast cancer. Clin Cancer Res 2007;13:1623-4.
2. Tsukada Y, Fouad A, Pickren JW, et al. Central nervous system metastasis from breast carcinoma. Autopsy study. Cancer 1983;52:2349-54.
3. Patanaphan V, Salazar OM, Risco R. Breast cancer: metastatic patterns and their prognosis. South Med J 1988;81:1109-12.
4. Hagemeister FB Jr, Buzdar AU, Luna MA, et al. Causes of death in breast cancer: a clinicopathologic study. Cancer 1980;46:162-7.
5. Cho SY, Choi HY. Causes of death and metastatic patterns in patients with mammary cancer. Ten-year autopsy study. Am J Clin Pathol 1980;73:232-4.
6. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003;97:2972-7.
7. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011;17:4834-43.
8. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10:1037-44.
9. Pestalozzi BC, Zahrieh D, Price KN, et al. Identifying breast cancer patients at risk for Central Nervous System (CNS) metastases in trials of the International Breast Cancer Study Group (IBCSG). Ann Oncol 2006;17:935-44.
10. Kallioniemi OP, Holli K, Visakorpi T, et al. Association of c-erbB-2 protein over-expression with high rate of cell proliferation, increased risk of visceral metastasis and poor long-term survival in breast cancer. Int J Cancer 1991;49:650-5.
11. Gabos Z, Sinha R, Hanson J, et al. Prognostic significance of human epidermal growth factor receptor positivity for the development of brain metastasis after newly diagnosed breast cancer. J Clin Oncol 2006;24:5658-63.
12. Christodoulou C, Bafaloukos D, Linardou H, et al. Temozolomide (TMZ) combined with cisplatin (CDDP) in patients with brain metastases from solid tumors: a Hellenic Cooperative Oncology Group (HeCOG) Phase II study. J Neurooncol 2005;71:61-5.
13. Addeo R, De Rosa C, Faiola V, et al. Phase 2 trial of

temozolomide using protracted low-dose and whole-brain radiotherapy for nonsmall cell lung cancer and breast cancer patients with brain metastases. Cancer 2008;113:2524-31.
14. Siena S, Crinò L, Danova M, et al. Dose-dense temozolomide regimen for the treatment of brain metastases from melanoma, breast cancer, or lung cancer not amenable to surgery or radiosurgery: a multicenter phase II study. Ann Oncol 2010;21:655-61.
15. Viñolas N, Graus F, Mellado B, et al. Phase II trial of cisplatinum and etoposide in brain metastases of solid tumors. J Neurooncol 1997;35:145-8.
16. Franciosi V, Cocconi G, Michiara M, et al. Front-line chemotherapy with cisplatin and etoposide for patients with brain metastases from breast carcinoma, nonsmall cell lung carcinoma, or malignant melanoma: a prospective study. Cancer 1999;85:1599-605.
17. Cassier PA, Ray-Coquard I, Sunyach MP, et al. A phase 2 trial of whole-brain radiotherapy combined with intravenous chemotherapy in patients with brain metastases from breast cancer. Cancer 2008;113:2532-8.
18. Ekenel M, Hormigo AM, Peak S, et al. Capecitabine therapy of central nervous system metastases from breast cancer. J Neurooncol 2007;85:223-7.
19. Chargari C, Kirova YM, Diéras V, et al. Concurrent capecitabine and whole-brain radiotherapy for treatment of brain metastases in breast cancer patients. J Neurooncol 2009;93:379-84.
20. Liang K, Lu Y, Jin W, et al. Sensitization of breast cancer cells to radiation by trastuzumab. Mol Cancer Ther 2003;2:1113-20.
21. Chargari C, Idrissi HR, Pierga JY, et al. Preliminary results of whole brain radiotherapy with concurrent trastuzumab for treatment of brain metastases in breast cancer patients. Int J Radiat Oncol Biol Phys 2011;81:631-6.
22. Polli JW, Olson KL, Chism JP, et al. An unexpected synergist role of P-glycoprotein and breast cancer resistance protein on the central nervous system penetration of the tyrosine kinase inhibitor lapatinib (N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine; GW572016). Drug Metab Dispos 2009;37:439-42.
23. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 2013;14:64-71.
24. Lin NU, Eierman W, Greil R, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. J Neurooncol 2011;105:613-20.

Cite this article as: Torrejón D, Di Cosimo S. Brain metastases in HER2-positive breast cancer: challenges and opportunities. Ann Palliat Med 2012;1(3):195-197. DOI: 10.3978/j.issn.2224-5820.2012.10.11

